

Marrow as Origin, Incubator and Reservoir: A Systems Oncology Model of Breast Cancer

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Abstract:

This article explores the hypothesis that the bone marrow serves as the primary origin and regulatory hub for systemic cancer processes, particularly in hormone-sensitive malignancies such as breast cancer. The integration of evidence from hematopoietic stem cell biology, clonal hematopoiesis, dormancy research and endocrine-immune-marrow crosstalk, can provide a conceptual framework in which disseminated progenitor cells initiate malignancy remotely from the primary tumor site. This article will contrast the prevailing epithelial-origin model, assess empirical support and propose future research directions. This perspective redefines cancer initiation, progression and treatment, reframing systemic equilibrium—not tumor eradication—as the therapeutic goal.

keywords:

marrow-origin cancer model; marrow-centric cancer model; tumor-centric cancer model; breast cancer; systems oncology; stem cell niche; trabecular bone; immune-marrow interaction; terrain theory; endocrine-marrow axis; dormancy and reactivation; tumor mutational burden; tumor heterogeneity; inflammatory breast cancer; invasive lobular carcinoma; clonal dissemination; cancer ecosystem

1. Introduction

The conventional model of breast cancer suggests that epithelial cells accumulate somatic mutations in a localized progression from *in situ* carcinoma to regional and distant metastasis. This tumor-centric model, while clinically dominant, struggles to explain key phenomena including early dissemination, long-term dormancy, non-sequential metastasis and resistance evolution. In contrast, a marrow-origin hypothesis proposes that certain malignancies originate not in local epithelium but in marrow-derived progenitors, including hematopoietic stem cells (HSCs), mesenchymal stem/stromal cells (MSCs), or immune myeloid precursors. These cells disseminate early, undergo reprogramming in distant niches such as breast tissue and form tumors as late-stage expressions of systemic dysregulation.

2. Historical and Theoretical Foundations

Paget's 1889 "seed and soil" theory introduced the idea of non-random metastasis. The "seed" represents the metastatic cancer cells and the "soil" represents the organ microenvironment that supports or permits tumor growth. Metastasis occurs only when the seed finds its way to an organ whose microenvironment favors tumor cell colonization and growth.

Halstead's 1894 "local" theory posited that breast cancer is local-regional disease that spreads in a contiguous, orderly fashion from the primary tumor through the lymphatic system to regional lymph nodes before metastasizing to distant sites. He believed that cancer cells were initially trapped by the lymph nodes, which acted as a barrier, and only when these nodes were overwhelmed could the cancer spread further. This theory was the basis for progressively disfiguring local surgeries, in an attempt to radically excise breast cancer 'from its roots'.

Boveri's 1914 "somatic mutation" theory postulated that cancer arises from genetic mutations in somatic cells which lead to uncontrolled cell division and tumor formation. This theory assumes cancer arises in the tissue of diagnosis (e.g., breast epithelium), focuses on genetic mutations and supports localized linear progression (Stage I → IV).

Fisher's 1970 "systemic hypothesis" of breast cancer posited that it is a systemic disease from its inception, rather than a localized growth that spreads in a predictable linear fashion. He argued that cancer cells disseminate early, even before a tumor is clinically detectable, undermining the logic of radical local surgery. Fisher's trials (e.g., NSABP) demonstrated that less extensive surgery (e.g., lumpectomy) was as effective as radical mastectomy, implying that local control does not affect survival. He challenged the Halstedian linear model (local → regional → distant). Fisher focused on dissemination as an early event but did not propose an alternative site of origin. His hypothesis also lacked a stem cell or evolutionary framework.

The "marrow-centric" model can be seen as a biological elaboration and mechanistic substantiation of Fisher's systemic hypothesis—providing a theoretical foundation that explains not only why breast cancer behaves systemically, but how it originates, evolves and disseminates in the context of the body's stem cell ecology. It also accommodates somatic mutations, but reframes them as downstream consequences of systemic niche instability rather than primary causes. And the "soil" becomes a downstream milieu that determines phenotype expression—receptor profile, proliferative capacity, dormancy/invasion potential.

3. Biological Rationale for the Marrow-Centric Model

The marrow is more than a passive environment; it is a dynamic, pluripotent platform capable of supporting every stage of cancer biology. This includes initiation, dormancy, therapeutic resistance and recurrence. Its unique properties distinguish it from all other potential tissue environments and affirm its central role in a systemic, progenitor-driven model of breast cancer.

3.1 Stem Cell Infrastructure: The Primordial Platform

The bone marrow serves as the adult body's central repository for both hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). These reside in tightly regulated microenvironments, including endosteal and perivascular niches, which maintain cellular quiescence, lineage plasticity and immune tolerance. These niches provide the perfect ecological context for malignant progenitor cells to emerge. Tumor-initiating cells may exploit these homeostatic mechanisms to remain dormant, undetected, or even to reprogram themselves epigenetically toward malignant transformation.

3.2 Immunological Modulation and Escape

Unlike the immune-vigilant architecture of the lung or liver, the marrow is immunologically permissive. It is densely populated with regulatory T cells, myeloid-derived suppressor cells (MDSCs) and tolerogenic cytokines. These features facilitate immune evasion and long-term survival of aberrant or pre-malignant cells. This immunosuppressive microenvironment can sustain dormant cancer progenitors for years—potentially decades—before systemic triggers or niche alterations reactivate them.

3.3 Hypoxic and Metabolically Plastic Microenvironment

The marrow is metabolically diverse and structurally compartmentalized. Hypoxia and acidic pH in certain marrow regions select for resilient, low-metabolism, slow-cycling cells—hallmarks of both stem cells and dormant cancer cells. The trabecular bone architecture provides both physical shelter and niche heterogeneity, which protect and isolate small clonal populations. This environment acts as a crucible for the selection of therapy-resistant or phenotypically aggressive clones.

3.4 Trafficking Interface: A Systemic Distribution Hub

Bone marrow is not a static reservoir. HSCs and progenitor cells routinely enter and exit the marrow via circulatory routes. This built-in traffic system allows early dissemination, reseeding of distant organs and bidirectional cellular migrations. This stands in contrast to the lung or liver, where stem-cell trafficking and niche reintegration are rare. The marrow's role as a

systemic trafficking hub makes it central not only to early dissemination but also to recurrence and metastasis.

3.5 Evolutionary Reservoir: The Cradle of Clonal Drift

As a long-term incubator, the marrow supports co-existence of heterogeneous tumor subclones. These cells engage in dynamic interactions with stromal elements, immune cells and extracellular matrix proteins. This ecosystem promotes selection of adaptive phenotypes, therapeutic resistance and phenotypic drift over time—features consistent with observations in metastatic breast cancer and multiple myeloma. The marrow's microanatomy and metabolic conditions make it a high-fidelity evolutionary platform.

3.6 Comparative Framework

Feature	Bone Marrow	Lung/Liver
Stem cell niche	Rich in HSCs and MSCs	Absent or less defined
Immune surveillance	Tolerant, immunosuppressive	Active immune filtering
Dormancy support	Strong (via hypoxia, niche signaling)	Weaker (more inflammation, less niche control)
Trafficking interface	HSC exit and reseed common	Rare stem cell migration
Evolutionary potential	High clonal adaptability in niche	Less structured clonal evolution

3.7 Supporting Evidence

Research suggests that Clonal Hematopoiesis (CHIP) mutated hematopoietic clones increase risk for solid tumors (Jaiswal et al., 2014). Bone marrow-derived MSCs show epithelial transdifferentiation in various tissues and contribute to tumor stroma (Karnoub et al., 2007). Additionally, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), both marrow-derived, have been shown to promote immune evasion and metastasis (Gabrilovich et al., 2012).

4. Dormancy, Dissemination and Niche Biology

Endosteal and perivascular niches and microenvironments maintain stem cell quiescence and offer immune shelter. Cancer cells exploit CXCR4/SDF-1 signaling to enter and remain dormant. Systemic changes (inflammation, estrogen loss, bone degradation) destabilize these niches, leading to tumor reactivation. Warm autopsy data indicate that metastases often arise from other metastases, not the primary tumor, implying marrow or niche-based reseed (Husemann et al., 2008).

5. Evidence from Breast Cancer Subtypes and Epithelial Cancer Integration

Distinct subtypes of breast cancer—traditionally framed as epithelial anomalies—can be more accurately interpreted through a systems oncology lens. It lays the groundwork for reclassifying heterogeneous presentations (ILC, mixed tumors) as niche-specific expressions of systemic clonal instability, with implications for both origin and progression.

5.1 Invasive Lobular Carcinoma (ILC): A Systemic-Niche Malignancy

Invasive lobular carcinoma (ILC) presents a diagnostic and conceptual challenge under the tumor-centric model. Unlike ductal cancers, ILC often fails to form discrete masses, growing instead in a diffuse, single-file pattern that eludes detection on standard imaging. It is frequently multifocal, multicentric, bilateral and prone to late systemic recurrences. These features are typically attributed to E-cadherin loss, yet this molecular detail does not explain ILC's systemic behavior, niche-specific growth, or long dormancy periods.

The marrow-centric model offers a coherent alternative: ILC represents a form of systemic clonal misregulation expressed within hormonally sensitive lobular niches. Its non-cohesive growth reflects stromal niche failure rather than localized epithelial mutation. Multifocality and bilaterality suggest multiple marrow-derived progenitor seeding events, while late recurrence aligns with known mechanisms of marrow dormancy and niche escape. ILC's behavior is better explained by its systemic and ecologic dynamics than by conventional mutation theory.

ILC is reframed not as a stealthy variant of ductal carcinoma but as a paradigm of systemic progenitor misregulation, manifesting through niche failure, dormancy escape and terrain-conditioned growth patterns. Its diffuse, multifocal behavior is interpreted as an epiphenomenon of marrow-derived clonal activation and stromal permissiveness.

Accordingly, ILC may not be best addressed through lesion-centric detection and cytotoxic therapy. Instead, terrain-modulating strategies, hormonal stabilization and niche-preserving interventions may offer more biologically rational pathways for early detection and disease control.

5.2 Mixed IDC-ILC Tumors: A Test Case for Paradigm Comparison

Mixed ductal-lobular carcinomas exemplify the limitations of linear mutational theories and support the marrow-centric hypothesis. Their coexistence is interpreted as evidence of parallel clonal activation, niche-specific phenotypic expression and stromal divergence—not simple intratumoral heterogeneity.

Mixed invasive ductal and lobular carcinomas (IDC-ILC) challenge the tumor-centric model, which must explain them as divergent clonal outcomes of a single epithelial transformation. In this view, a common epithelial progenitor undergoes linear or branched mutations—some retaining E-cadherin (IDC), others losing it (ILC)—resulting in coexisting phenotypes. However, this fails to account for their spatial, behavioral and systemic heterogeneity.

The marrow-centric model interprets mixed tumors as distinct expressions of multiple marrow-derived progenitor clones responding to niche-specific signals. Rather than linear clonal evolution, these tumors arise from separate progenitors activated by systemic terrain cues. The ductal and lobular patterns reflect phenotypic plasticity conditioned by local stromal, hormonal and immune microenvironments. This model accounts for the coexistence of mass-forming and infiltrative behaviors and frames them as parallel outcomes of a disrupted systemic ecology.

Thus, mixed IDC-ILC tumors serve as diagnostic evidence for clonal diversity seeded from the marrow and shaped by terrain—not simply as an unusual histological variant, but as a hallmark of systemic niche instability.

Feature	Tumor-Centric Model	Marrow-Centric Model
Single origin theory	Monoclonal transformation + divergence	Multiple progenitor seeds with niche-specific expression
Explains mass vs. diffuse growth	Partially (via E-cadherin mutation)	Fully (as niche-conditioned phenotypic expression)
Considers terrain dynamics	No	Yes—key to clonal behavior
Reflects systemic disease	Minimally	Fully
E-cadherin loss	Lobular differentiation from mutated ductal cell	Expression of niche-specific progenitor phenotype

Coexistence in one lesion	Linear clonal divergence	Parallel clonal seeding and terrain-conditioned expression
Treatment implications	Treated as single clonal event	Requires recognition of systemic clonal diversity

5.3 Inflammatory Breast Cancer: A Phenotype of Terrain Collapse

Inflammatory breast cancer (IBC) is among the most aggressive and clinically perplexing forms of breast cancer, characterized by dermal lymphatic invasion, rapid progression, erythema and diffuse swelling—often without a discrete tumor mass on imaging. In the tumor-centric model, IBC is attributed to highly mutated epithelial clones that invade lymphatics and induce inflammation-like symptoms, though this framework struggles to explain its systemic onset, rapid dissemination and immunovascular disruption.

In contrast, the marrow-centric model interprets IBC as an expression of acute terrain collapse. It emerges from dysregulated marrow-derived progenitors, systemic immune suppression and vascular-niche failure. The skin manifestations are not just signs of local invasion but indicators of niche failure at the immune-vascular interface. IBC in this view is a systemic, niche-driven event that reflects catastrophic loss of dormancy control and stromal integrity. This model not only accounts for the absence of a palpable tumor but predicts the aggressive and system-wide progression observed in IBC. Therapeutically, IBC may require terrain stabilization strategies targeting the marrow-immune-vascular axis, rather than intensified local therapies alone.

Characteristic	Tumor-Centric Model	Marrow-Centric Model
Etiology	Aggressive epithelial mutation	Systemic niche collapse and immune-vascular breakdown
Dermal involvement	Tumor invasion of lymphatics	Myeloid dysfunction and endothelial niche reprogramming
Imaging visibility	Often massless and unexplained	Reflects diffuse stromal dysfunction and clonal infiltration
Treatment response	High-dose local and systemic therapy	Indicates urgent need for terrain stabilization

5.4 HR+ breast cancer, associated with long dormancy, high bone tropism and late recurrence, is compatible with marrow-derived initiation.

5.5 HER2+ and TNBC tends to be more aggressive and still display dormancy and niche behaviors, especially in the marrow.

5.6 Tumor-Agnostic Molecular Homogeneity is exemplified by HER2+ tumors in breast, lung, gastric and colon, which support a progenitor-based, not tissue-based, classification.

While breast cancer is especially heterogeneous, similar patterns are observed in other epithelial malignancies. Ovarian cancer, though typically peritoneal, shows marrow infiltration, macrophage-driven stroma formation and relapse patterns suggesting systemic progenitor involvement. Prostate cancer is nearly universally bone-tropic, interacting deeply with marrow niches. Colon and lung cancers may not originate in the marrow but engage it during metastasis or dormancy. These cancers, though traditionally viewed through an epithelial lens, often converge on marrow ecosystems for immune evasion, dormancy and relapse. Thus, the marrow-centric model provides a unifying framework across diverse solid tumors, especially in explaining their systemic behavior and therapeutic resistance.

The success of tumor-agnostic therapies like Enhertu (trastuzumab deruxtecan), which target HER2-expressing tumors regardless of anatomical origin, underscores a conceptual shift from organ-specific oncology to phenotype-driven systemic therapy. In the traditional tumor-centric model, HER2 expression is viewed as a result of tissue-specific mutations, with cancer classification based on the tumor's site of origin. Enhertu is thus interpreted as a precision therapy against a shared mutation target across distinct epithelial cancers.

In the marrow-centric systems oncology model, HER2+ tumors across breast, lung and gastric tissues are viewed not as parallel local accidents but as expressions of a shared clonal lineage—one disseminated through the marrow, capable of niche adaptation and conditionally expressing HER2 under permissive stromal or immune-endocrine signals. Enhertu's pan-tumor efficacy supports the view that cancer is a systemic progenitor disorder rather than a series of disconnected epithelial mutations.

This model explains not only the convergence of HER2 expression in diverse tissues but also the emergence of resistance as a form of subclonal terrain adaptation, rather than receptor escape alone. Thus, tumor-agnostic therapies align more naturally with a systemic paradigm in which clonal identity and niche context—not tissue histogenesis—define therapeutic relevance.

5.7 Genetic Mutations as Terrain Modifiers: BRCA, CHEK2 and MET in the Marrow-Centric Model

In the tumor-centric model, germline mutations such as BRCA1/2, CHEK2 and MET are treated as direct inducers of epithelial cancer due to impaired DNA repair or aberrant signaling. These mutations are assumed to increase the likelihood of somatic mutations accumulating in epithelial cells, which then form tumors in a linear, localized manner. However, this framework cannot explain the variable penetrance of these mutations, their tissue selectivity, or why only certain organs manifest malignancy.

The marrow-centric model interprets these mutations differently: as systemic modifiers of progenitor integrity, marrow niche resilience and immune-endocrine terrain regulation. BRCA1/2 mutations may impair DNA repair in hematopoietic or stromal progenitors, leading to clonal instability, early dissemination, or loss of dormancy control. CHEK2 mutations may similarly influence cell-cycle checkpoint fidelity within stem cell reservoirs. MET mutations can alter stromal or vascular signaling critical to progenitor containment. These mutations do not target the breast per se, but destabilize the systemic terrain that governs clonal containment, allowing breast cancer to emerge from marrow-derived cells in permissive niches.

Feature	Tumor-Centric Model	Marrow-Centric Model
Role of BRCA/CHEK2/MET	Localized risk enhancers (DNA repair defects)	Systemic regulators of progenitor resilience and terrain
Site specificity	Tissue-targeted epithelial vulnerability	Terrain-mediated niche selection (breast, ovary)
Penetrance variability	Poorly explained	Reflects variable systemic compensation or terrain stress
Immune and endocrine context	Largely ignored	Central to how mutations influence niche and clonal behavior

This recontextualization explains why not all mutation carriers develop cancer, why the cancers that do appear vary in timing and behavior, and why tissue selectivity is niche-driven rather than epithelium-intrinsic.

6. Resolving Clinical Paradoxes: Systems Oncology Versus Mutation Determinism

A key strength of the marrow-centric systems oncology model is its ability to resolve epidemiologic and clinical paradoxes that the somatic mutation model cannot easily explain. For example, approximately 85% of lung cancer patients have a history of smoking, yet ~85% of smokers never develop lung cancer. This contradiction is framed in the tumor-centric model as stochastic mutation or incomplete penetrance. In the marrow-centric view, smoking is understood as a terrain-disrupting agent—inducing oxidative stress, immune dysfunction and niche instability. Cancer arises not from exposure alone, but from the collapse of systemic clonal containment in susceptible individuals.

Comparable paradoxes exist in breast cancer:

Paradox	Tumor-Centric Interpretation	Marrow-Centric Explanation
Most DCIS does not progress	Mutation risk stratification unclear	Reflects successful terrain containment vs. reactivation potential
Late recurrence of HR+ tumors	Poorly understood dormancy	Reactivation of marrow-seeded clones via terrain collapse
Higher breast cancer rates in affluent populations	Screening bias or hormone therapy	Hormonal and terrain shifts predispose to niche instability
BRCA mutation \neq cancer inevitability	Incomplete penetrance	Terrain fragility determines expression, not mutation alone
Toxic therapy improves local control but not survival	Overtreatment explanation	Niche collapse and resistant subclonal evolution offset early benefits

These patterns support the notion that cancer is not solely a mutational event but an emergent property of terrain degradation. Restoring or maintaining marrow and immune system equilibrium may offer a path to both prevention and prolonged dormancy.

Comparative Plausibility

Criterion	Tumor-Centric Model	Marrow-Centric Model
Biological Coherence	High for local lesion formation; limited for systemic recurrence	High across stem cell dynamics, immune ecology, endocrine-immune integration
Alignment with Clonal Hematopoiesis	Indirect, often ignored	Directly incorporates as upstream mutational landscape
Explains Early Dissemination	Poorly explained; treated as anomalous	Integral feature; early systemic spread precedes tumor detection
Accounts for Dormancy Reactivation	Dormancy is under-theorized	Dormancy and reactivation are central regulatory processes
Relevance to Late Recurrence	Difficult to explain with residual disease concept	Predicted by reactivation of marrow-nurtured DTCs
Consistency with Warm Autopsy Data	Contradicted by metastasis-to-metastasis seeding	Supported; marrow as a re-seeding reservoir
Tissue Tropism and Metastasis Pattern	Attributed to anatomical drainage or random chance	Explained via niche compatibility and systemic terrain cues
Integration of Immune-Terrain Dynamics	Peripheral	Central to disease initiation and progression

Explanatory Power

Phenomenon	Tumor-Centric Model	Marrow-Centric Model
Early metastasis	Viewed as pathological anomaly	Explained as systemic dissemination of progenitors
Late recurrence (10+ years)	Attributed to missed residual cells	Explained as terrain-driven dormancy escape
Therapeutic paradoxes	Attributed to clonal resistance post-treatment	Viewed as terrain disruption reactivating dormant subclones
Non-sequential metastasis patterns	Contradicts linear progression	Explained via marrow-based polyclonal reseeding
Tumor heterogeneity	Result of late-stage mutation accumulation	Reflects diverse progenitor origins seeded from marrow
Lymph node involvement	Interpreted as metastatic gateway	Reframed as immune terrain marker, not a causative step
Tumor-agnostic therapy effectiveness	Requires ad hoc explanation	Expected from shared progenitor traits and niche compatibility

Predictive Capability

Aspect	Tumor-Centric Model	Marrow-Centric Model
Relapse risk assessment	Based on tumor stage, grade	Adds marrow niche status, clonal hematopoiesis, immune profile
Therapy response prediction	Based on tumor subtype	Integrates systemic terrain condition and bone integrity
Dormancy and recurrence forecast	Poor; assumes eradication or failure	Models risk based on terrain degradation or systemic shifts
Therapeutic planning	Emphasizes lesion removal or inhibition	Supports terrain-preserving and reprogramming strategies
Cross-cancer treatment generalizability	Limited by site specificity	Enhanced by shared marrow-origin dynamics and markers
Surveillance strategy development	Based on tumor imaging and residuals	Expanded to include marrow biomarkers and systemic indicators

Sidebar: Plausibility of a Marrow-Origin for All Breast Cancer Subtypes

A marrow-centric origin model for breast cancer posits that most phenotypes arise from disseminated bone marrow–derived progenitor cells—such as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), or myeloid progenitors. This model accounts for early dissemination, phenotypic plasticity, dormancy, bone tropism and therapeutic resistance.

Subtype	Marrow-Origin Plausibility	Rationale
ER+	Very high	Indolent, bone-tropic, endocrine-modulated phenotype
HER2+	High	Found across tissues; HER2 is phenotypically inducible
Triple-negative (TNBC)	High	Inflammatory, immune-evading, systemically unstable
Triple-positive (TPBC)	Very high	Mixed phenotype; implies systemic receptor programming

Inflammatory Breast Cancer	Very high	Rapid dissemination, vascular niche failure
Multifocal/Multicentric	High	Discontinuous foci suggest early clonal dissemination
Pure DCIS (localized)	Moderate to low	May be true epithelial-limited, indolent lesions in some cases

Estimated Marrow-Centric Model Spectrum:

- Marrow-origin dominant: ~70–80% of cases
- Mixed origin (systemic + local): ~15–20%
- Strictly local epithelial: ~5–10%

This spectrum suggests that while not all breast cancers may originate in the marrow, the majority do—and that subtype expression is best understood as niche-driven phenotypic divergence.

Sidebar: Primary Peritoneal Cancer and the Marrow-Origin Hypothesis

Primary peritoneal cancer (PPC) behaves nearly identically to high-grade serous ovarian carcinoma (HGSOC), despite sometimes occurring in the absence of a detectable ovarian mass or even in men. Both cancers share histologic features, treatment protocols and dissemination patterns—typically presenting with widespread peritoneal involvement rather than a localized primary lesion. This creates a paradox for the classical model, which posits a fallopian tube or ovarian surface epithelium origin.

The marrow-origin framework resolves this paradox by proposing that ovarian and peritoneal cancers are systemic diseases that emerge from disseminated, marrow-derived progenitor cells. These progenitors may home to immune-privileged, hormonally responsive niches like the peritoneum or ovary, where epithelial-mesenchymal plasticity, immune modulation and hormonal milieu allow for malignant transformation.

Under this model:

- PPC is not a rare exception but a revealing expression of the systemic nature of “ovarian” cancer.
- The peritoneum acts as a receptive terrain rather than a secondary spread site.
- The presence of PPC in men, and its occurrence post-oophorectomy in women, supports the notion that the ovary is not the disease origin but one of several possible expression zones.

Thus, PPC becomes a clarifying case for a systems-based reinterpretation of ovarian cancer. Like breast cancer in the marrow-centric model, the disease arises not from local epithelial missteps, but from systemic progenitor dynamics shaped by terrain permissiveness, immune evasion and clonal evolution.

7. Therapeutic and Diagnostic Implications

7.1 Hormonal Terrain Therapies: Estradiol and progesterone support marrow, immune and vascular homeostasis.

7.2 Reassessment of Systemic Therapies: Chemotherapy, radiation and anti-estrogens degrade marrow niches and may foster resistance.

7.3 Marrow-Based Biomarkers: Profiling marrow-resident progenitors and immune cell

dynamics may predict risk and recurrence.

7.4 Vaccine Strategies: mRNA vaccines might reprogram marrow niches or suppress early clonal expansion.

7.5 Tumor Mutational Burden (TMB) as a Marrow-Terrain Danger Signal

Within the marrow-centric systems oncology framework, high tumor mutational burden (TMB) is reinterpreted not as a mere genomic feature of tumor aggressiveness or immunogenicity, but as a systemic "danger signal"—a biomarker of terrain collapse. Elevated TMB may reflect dysfunction in marrow-derived progenitor regulation, immune surveillance failure and endocrine or metabolic instability.

Mechanisms include:

- Clonal hematopoiesis–induced immune dysregulation, reducing effective neoantigen clearance.
- Marrow niche degradation, releasing unstable progenitors with epigenetic plasticity.
- Expansion of immunosuppressive myeloid populations (MDSCs, TAMs) impairing tumor immune editing.
- Loss of hormonal modulators (estradiol, progesterone) that maintain genomic fidelity and immune tolerance.

In this view, high TMB should not be seen solely as a predictive biomarker for immune checkpoint blockade, but as a late-stage manifestation of upstream systemic failure. Combined profiling of TMB with marrow biomarkers and terrain indicators may better stratify risk and guide restorative interventions.

Sidebar: Rethinking Tumor Burden and Mutation Burden in a Systems Oncology Framework

Traditional oncology often reduces tumor burden to a single "index" lesion and defines tumor mutational burden (TMB) genomically. This underestimates the true complexity of multifocal or phenotypically heterogeneous cancers. A marrow-centric, systems-level perspective redefines these metrics:

Concept	Traditional View	Systems Oncology Perspective
Tumor Burden	Mass of index tumor	Cumulative volume of all malignant lesions
Tumor Mutational Burden	Mutations/megabase from sequencing	Observable phenotypic diversity and subclonal plasticity
Multifocal Heterogeneous Tumors	Not fully stratified; treated as a singular entity	Evidence of systemic progenitor misregulation and evolutionary diversity

In patients with co-occurring HER2+/HR– and HER2–/HR+ tumors, both the total tumor volume and the functional mutation burden are higher than acknowledged by conventional models. These represent systemic clonal dysregulation, not isolated anomalies. Incorporating total tumor architecture and clonal phenotype diversity into burden assessments aligns more closely with real-world cancer behavior and supports a shift toward terrain-based risk stratification and therapeutic design.

While TMB is genomically defined and selectively measured in advanced or metastatic settings, phenotypic heterogeneity—such as co-occurrence of HER2+/HR– and HER2–/HR+ tumors—signals clonal diversity and epigenetic plasticity. These phenotypic variations,

although not quantified as TMB, reflect similar upstream systemic dysregulation and may serve as functional equivalents of genomic burden within the marrow-centric framework.

Concept	Definition	Measurement	Clinical Relevance
Tumor Mutational Burden (TMB)	Total somatic mutations/megabase	Genomic sequencing	Immunotherapy prediction
Phenotypic Heterogeneity	Receptor or behavior variation	Histopathology, Immunohistochemistry	Therapeutic complexity
Multifocal Heterogeneous Tumors	Spatially and molecularly distinct tumors	Imaging + pathology	Suggests polyclonality, high evolutionary capacity

7.6 Research Priorities

- Develop non-invasive marrow imaging and biomarker panels.
- Longitudinal studies on clonal hematopoiesis in relation to solid tumors.
- Marrow-centric preclinical models of cancer initiation.

8. Conceptual Challenges and Paradigm Resistance

Evidence for a marrow origin is obscured by lesion-centric research models, lack of lineage tracing in humans and funding biases. Yet the model aligns with systemic biology, early dissemination and terrain-based cancer dynamics.

8.1 Clinical Case Illustration: Bilateral, Phenotypically Divergent Tumors as a Marrow-Centric Signature

A patient presents with bilateral breast tumors showing striking heterogeneity: a HER2+ HR– grade 3 IDC tumor in the right breast and HER2– HR+ grade 1 and 2 mixed IDC/ILC tumors in the left breast—20 years after treatment for left-sided DCIS with lumpectomy, radiation and 5 years of tamoxifen. Tumor sizes range from ~1 to 1.5 cm, but their doubling times vary from months to years. This scenario exemplifies temporal, spatial, morphologic and phenotypic heterogeneity.

In a conventional tumor-centric model, this presentation would be treated as a recurrence or multiple primary tumors. However, the marrow-centric model interprets this presentation as a sign of systemic progenitor instability and clonal plasticity. The diversity in tumor grades, morphology and receptor statuses implies multiple marrow-derived subclones, activated in distinct tissue niches under varying systemic conditions. Prior radiation and endocrine therapy may have disrupted niche integrity, contributing to long-term dormancy escape and reseeding.

This case illustrates the limitations of targeting a single lesion or pathway and underscores the need for terrain-restorative, marrow-supportive strategies. It supports the notion that breast cancer, particularly when temporally and phenotypically complex, is not a localized disease but a systemic expression of marrow dysregulation.

Therapeutically, this complexity is compounded by rapid trabecular bone degradation observed during two years of biannual zoledronic acid infusions, with a QCT lumbar T-score declining from –3.5 to a trabecular bone score (TBS) adjusted lumbar T-score of –4.4. Such severe degradation is inconsistent with the expected protective effect of Zometa and suggests aggressive metastatic colonization and clonal niche disruption. Zometa suppresses osteoclast activity, which disrupts the coupled remodeling dynamics between osteoclasts and osteoblasts. This not only impairs repair and leads to microdamage accumulation, but also results in hypermineralized, metabolically inert and mechanically brittle bone. In this sense, Zometa causes mechanical degradation of trabecular architecture—particularly in high-

turnover regions like the lumbar spine—by freezing remodeling, degrading microarchitectural flexibility and disrupting marrow-stromal-vascular integration. Continued Zometa use in this context may exacerbate niche failure by preserving structurally dense but functionally impaired bone and impeding necessary adaptive remodeling and marrow support.

Denosumab (monoclonal antibody antiresorptive agent) or anabolic agents (teriparatide, romosozumab) are similarly contraindicated or of uncertain benefit, as they either further suppress critical pathways or risk stimulating malignant clonal activity. The potential benefit of transdermal estradiol and oral progesterone depends critically on the integrity of residual niche elements—osteoblasts, vasculature, stromal precursors—which may already be too compromised to support recovery. Thus, in this case, marrow stabilization is theoretically desirable but biologically unlikely under continued systemic toxicity or advanced architectural collapse.

DEXA T-score improvements may mask underlying trabecular degradation, especially in marrow-degraded terrain, as revealed by QCT and TBS metrics.

Metric	2023	2025	Interpretation
DEXA T-score	-3.3	-3.1	Apparent improvement in areal BMD
QCT	-3.5	— — —	Severely degraded trabecular bone vBMD
DEXA TBS (adjusted)	— — —	-4.4	Critical loss of trabecular architecture

8.2 Rethinking 'Recurrence' vs. 'New Primary' in the Marrow-Centric Model

In conventional oncology, a tumor is labeled a “recurrence” if it reemerges at or near the site of a previous malignancy and a “new primary” if it arises in a different quadrant or the contralateral breast with a different receptor profile. This lesion-centric framework assumes localized transformation events as independent origins.

The marrow-centric systems model fundamentally redefines this distinction. Recurrence is viewed as the reactivation of dormant, marrow-derived progenitor cells or micrometastatic clones within permissive niches, while new primaries are reframed as distinct expressions of systemic progenitor instability—often seeded from related or epigenetically divergent marrow clones. The receptor heterogeneity or temporal gap between tumors does not imply independence but may reflect niche-driven plasticity, therapy-induced selection, or terrain collapse. Therefore, both “recurrence” and “new primary” are seen as systemic manifestations of clonal terrain dysregulation, differing more in context than in kind.

This reinterpretation has major implications: tumors emerging decades apart or in anatomically distinct sites may not be biologically independent. Instead, they may signal a continuous failure of systemic clonal control—a dynamic evolution of marrow-origin disease, not a series of isolated mutational events.

8.3 Tumors as Markers, Not Origins – A Systemic Interpretation of Phenotypic Emergence

The appearance of multifocal, HER2+ HR– grade 3 tumors in the previously untreated right breast may not reflect a local mutational event. Instead, it likely indicates a recent change in terrain that enabled the emergence or reseeding of an aggressive, systemically evolved clone. Potential contributors include hormonal collapse, immune suppression, metabolic dysfunction, or vascular remodeling—all of which can reconfigure the breast niche into a permissive soil for dormant or migrated progenitor cells.

This supports a broader paradigm shift: breast tumors should be viewed not as primary loci of origin but as diagnostic markers of systemic clonal instability. In this model, tumors are

expressions of underlying systemic failure—reflecting where progenitor cells have found conditions favorable for phenotype expression. As with metastasis-to-metastasis spread observed in warm autopsies, clonal evolution and reseeding may originate from distant niches (e.g., lung, liver, marrow) and reappear in the breast.

This interpretation reorients clinical strategy: the goal is not merely tumor eradication but terrain stabilization, immune modulation and clonal containment. Local tumors become visible manifestations of a larger, invisible systems pathology.

8.4 Temporal and Spatial Divergence in Bilateral Breast Cancer

This bilateral case illustrates how terrain conditions, treatment history and clonal dormancy interact over time in a marrow-centric framework. The left breast, previously treated with radiation and tamoxifen, developed multifocal ER+ PR+ mixed IDC/ILC tumors—20 years after treatment. Meanwhile, the right breast, previously untreated, developed HER2+ HR– Grade 3 tumors over what appears to be a shorter timeframe.

In this model, the breasts are not independent origins, but distinct soil environments shaped by systemic and local conditions. The left breast, following radiation, likely underwent fibrotic, immune-modulated remodeling. This niche eliminated aggressive clones but allowed dormant, HR+ progenitors to slowly reemerge. The mixed morphology (IDC/ILC) suggests stromal disruption and lineage plasticity induced by radiation.

Conversely, the right breast, unmodulated by prior treatment, remained a fertile niche. There, HER2+ HR– tumors likely arose from either recent seeding of an evolved progenitor or reawakening of a dormant clone shaped by aging terrain, metabolic stress, or immune drift. This temporal and spatial heterogeneity exemplifies a non-linear, systemic model of cancer evolution—where early marrow seeding, niche remodeling and immune-hormonal conditions determine tumor phenotype, not local mutational accidents.

9. Therapeutic Implications in Advanced Terrain-Disrupted Disease

In cases of advanced, heterogeneous, or bilaterally multifocal breast cancer, where systemic dissemination has likely occurred, the marrow-centric model still offers conceptual clarity—but imposes a critical reassessment of what therapeutic modulation is realistically possible. While marrow niches are biologically dynamic, their clinical modulation is severely limited in patients actively receiving systemic cytotoxic therapies. Chemotherapy, radiation, targeted endocrine deprivation and other conventional treatments impose continuous damage on the marrow environment—eroding niche integrity, immune equilibrium and progenitor homeostasis.

Thus, meaningful niche restoration or terrain stabilization is only plausible if such toxic interventions are withdrawn, paused, or avoided entirely. In their continued presence, attempts to restore marrow quality are likely neutralized or reversed. For terrain-based strategies—such as physiologic hormone replacement or immune-metabolic stabilization—to have any effect, the therapeutic objective must shift away from eradication and toward systemic containment. Otherwise, optimism about late-stage niche modulation becomes a contradiction in terms.

10. The Marrow's Dual Role: Origin and Evolutionary Incubator

In the marrow-centric model, the bone marrow plays a multiphasic role in the development, evolution and systemic dissemination of breast cancer. Initially, it acts as the origin point—a dynamic environment where progenitor cells such as HSCs, MSCs, or myeloid precursors are shaped by hormonal, inflammatory, or mutational stress. These progenitors may acquire features that predispose them to dormancy escape, immune evasion, or migratory behavior. Upon dissemination to peripheral tissues like the breast, the local terrain (the “soil”) determines phenotypic expression. This includes receptor profile (ER, HER2, etc.), proliferative capacity

and potential for dormancy or invasion. The tumor phenotype thus arises not only from the cell's lineage but also from the contextual cues of the stromal, endocrine and immune microenvironment.

In advanced disease stages, the marrow reactivates as an incubator for evolved subclones. It becomes a site for:

- Ongoing subclonal diversification under treatment pressure
- Reservoir of metastasis-associated immune cells (e.g., MDSCs, TAMs)
- Recirculation and reseed to distant organs, contributing to heterogeneity and resistance

Sidebar: Paradox of Age and Aggression

A key question for the marrow-centric model is how to reconcile the observation that aggressive breast cancers are more common in younger women with “healthier” marrow, while older, postmenopausal women—with hormonally degraded and fibrotic marrow—more often present with indolent, slow-growing tumors. And why, hormone replacement therapy provides a breast cancer mortality benefit to hormone deficient menopausal women.

In premenopausal women, high levels of endogenous hormones exist in a biologic context of dynamic marrow activity, high immune plasticity and regenerative niche environments. In such a milieu, if a disseminated progenitor clone gains proliferative autonomy or immune invisibility, hormones can paradoxically support aggressive progression. In contrast, postmenopausal women experience a hormone-deficient and destabilized terrain. Here, physiologic repletion of estradiol and progesterone restores marrow niche integrity, immune regulation and systemic homeostasis—effectively lowering the risk of malignant emergence or aggressive evolution.

Estradiol and progesterone do not merely stimulate proliferation. They also regulate apoptosis, differentiation and immune function. In a deficient terrain, hormone replacement therapy reintroduces these homeostatic controls, reducing unchecked growth in hormone-sensitive clones and potentially preventing clonal drift toward more aggressive phenotypes. Studies show that breast cancers in HRT users tend to be well-differentiated, HR+ and less aggressive. These features suggest that terrain restoration via HRT supports more regulated, nonlethal phenotypic expressions of disseminated clones.

HRT contributes to the preservation of trabecular bone and marrow quality—an essential substrate for immune and stem cell equilibrium. This stabilization likely prevents the emergence of mutagenic, immunosuppressive, or pro-metastatic niches, thereby delaying or avoiding cancer progression altogether.

In marrow-centric terms, estradiol + progesterone in young women can amplify unregulated proliferation when malignancy escapes control, but in menopausal women, the same hormones act to restore systemic balance.

11. Phenotypic Divergence from a Common Progenitor

Breast cancer subtypes—ER-positive, HER2-positive, triple-negative and inflammatory—are traditionally treated as distinct diseases, defined by receptor expression profiles and local mutational pathways. However, within a marrow-centric systems oncology model, these phenotypes are better understood as context-specific manifestations of a shared, systemic progenitor origin.

Consider that all major breast cancer subtypes may arise from bone marrow-derived progenitor cells—such as mesenchymal stem cells (MSCs), myeloid-derived suppressor cells

(MDSCs), or hematopoietic progenitors. These cells disseminate early and seed epithelial tissues like the breast, where local niche conditions—immune tone, hormonal signals, stromal composition and vascular integrity—determine their phenotypic expression.

- ER+ tumors emerge in estrogen-rich, immune-quiescent microenvironments.
- HER2+ tumors reflect adaptive responses to growth factor dysregulation and hypoxia.
- Triple-negative breast cancers (TNBC) arise in inflammatory, immunosuppressed, or adipose-altered terrains.
- Triple-positive breast cancers (TPBC) reflect co-activation of multiple receptor pathways in unstable or convergent niches.
- Inflammatory breast cancer (IBC) signals acute niche collapse, endothelial reprogramming and immune escape.

These phenotypes can coexist or evolve over time, depending on systemic clonal evolution and niche feedback. Rather than indicating distinct origin events, they are phenotypic divergences of a common, marrow-derived lineage, shaped by terrain and therapeutic pressure. This view reframes breast cancer not as a group of genetically isolated entities, but as a dynamic clonal diaspora—emerging from the marrow, incubating in systemic niches and expressing heterogeneity in response to evolving local and systemic ecologies.

12. Genetic Modulation of Progenitor Dynamics in a Marrow-Centric Model

Conventional oncology often interprets germline mutations such as BRCA1/2, CHEK2, or MET as site-specific initiators of breast cancer. In contrast, the marrow-centric model repositions these mutations as modulators of systemic clonal behavior, primarily affecting bone marrow progenitor fitness, dormancy and migratory potential.

Mutations in BRCA1/2 impair DNA repair mechanisms, increasing genomic instability within hematopoietic or mesenchymal progenitor cells. CHEK2 disruption reduces DNA damage checkpoints, allowing error-prone clones to escape elimination. MET mutations drive growth factor signaling, promoting progenitor expansion, tissue migration and niche colonization. These mutated progenitors, when exposed to permissive terrain—defined by endocrine signals, immune tone and stromal integrity—differentiate into context-specific cancer phenotypes (ER+, HER2+, TNBC, etc.).

Thus, mutations shape progenitor potential and terrain interaction, not just tumor behavior. They do not act as deterministic triggers at the tumor site but rather as systemic influencers of clonal evolution, immune evasion and phenotype expression.

The marrow-centric model supports a non-linear model of tumor development: mutations bias systemic progenitors toward instability and dissemination, while local microenvironments dictate whether and how those cells evolve into clinical cancer.

13. Conclusion

The marrow-centric model represents a paradigm shift in cancer biology. By framing malignancy as a failure of progenitor regulation and niche integrity rather than isolated mutation, it offers new avenues for prevention, detection and therapy. Systems-oriented, terrain-preserving interventions—particularly hormone and immune-stabilizing agents—may be key to managing indolent or preclinical disease.

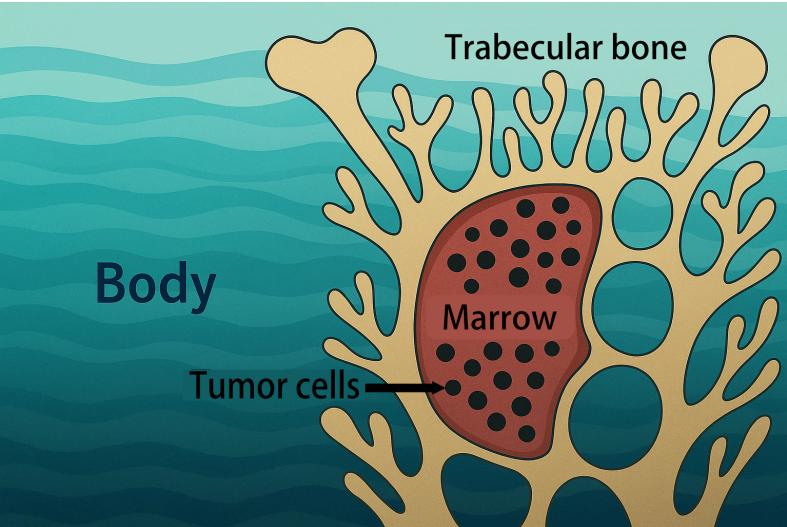
Furthermore, the observation of phenotypically heterogeneous, multifocal tumors within a single patient highlights a concept of *functional mutation burden*—a form of systemic clonal complexity not captured by genomic sequencing alone. In the marrow-centric model, such diversity arises not from linear local evolution but from marrow-derived progenitor

misregulation, terrain degradation and therapy-driven niche collapse. This heterogeneity signals a higher evolutionary capacity, therapeutic resistance and potential for late, intractable disease.

These insights demand a shift in cancer assessment and treatment strategy: from tumor eradication to systemic restoration. Early detection of marrow instability, hormonal terrain decline and immune dysfunction may offer more promise in controlling cancer than traditional lesion-focused paradigms. Functional mutation burden should thus be seen not only as a prognostic marker, but as a systemic warning—one best addressed by stabilizing the terrain rather than escalating the assault.

The 'Coral Reef' Metaphor: A Systemic Analogy for Marrow-Centric Cancer Ecology

Consider a metaphor: the trabecular bone and marrow represent a coral reef, cancer cells are an invasive species and the body is the ocean that surrounds and nourishes both. Just as coral reefs are complex, interdependent ecosystems vulnerable to environmental shifts, the bone marrow and its niches are dynamic structures sustaining immune regulation, progenitor cell homeostasis and systemic resilience. Cancer emerges not merely as a local mutational accident but as an invasive biological expression of ecological imbalance within the reef.



Component	Metaphor	Biological Counterpart
Coral reef	Trabecular bone and marrow	Structural and metabolic substrate for niche function
Invasive species	Cancer cells	Clonal progenitors disrupting local ecology
Ocean	Systemic body environment	Endocrine, immune and metabolic terrain
Reef destruction by toxins	Chemotherapy/ radiation	Treatment-induced niche collapse and immune impairment
Oceanic changes	Hormonal/immune shifts	Systemic modifiers of niche stability and clonal behavior

Current cancer treatments—chemotherapy, radiation, endocrine blockade—are akin to dumping toxic chemicals onto a fragile reef to eliminate the invasive species. While some

cancer cells may be eradicated, the collateral damage often includes the destruction of the coral ecosystem itself, impairing its regenerative capacity and potentiating further instability.

Moreover, the changing conditions of the ocean—the body’s endocrine, immune and metabolic terrain—shape both the emergence of the cancerous “species” and the reef’s capacity to respond to therapeutic stressors. In this metaphor, enduring cancer control emerges not from scorched-earth tactics but from restoring the health and resilience of the reef.

Epilogue: On Seeing Differently – Paradigm Shift from the Outside In

The marrow-centric model of breast cancer—and its broader implications for systems oncology—emerged not from within the prevailing medical orthodoxy but from a position of critical synthesis across disciplines. The dominant paradigm in oncology remains rooted in organ-centric staging, linear progression models and a reductionist approach that fragments biology into targetable compartments.

Within this tumor-centric framework, paradoxes are not signals of deeper systemic processes but are instead labeled as exceptions, anomalies or outliers. Recurrence is interpreted as failure of eradication, not re-expression of systemic instability. Primary peritoneal cancer is treated as ovarian cancer. Treatments that induce dormancy breakdown, immune depletion, or clonal selection are deployed in the name of tumor control—without re-evaluating whether the tumor is even the true locus of disease.

To see the contradictions is to reject the illusion of linearity. It is to notice that breast cancers often appear decades after initial dissemination. That endogenous or treatment induced bone marrow degradation and immune drift precede malignant transformation. That multifocal, bilateral, or phenotypically divergent tumors are not coincidental but systemic expressions.

Such insights do not arise from increasing specialization, but rather from a multidisciplinary perspective. They require a willingness to reanalyze data from a new frame of reference, to look at cancer not as a battle against a tumor, but as a systems failure of terrain, regulation and progenitor containment.

This article is not merely a critique of existing dogma—it is a proposal for conceptual restructuring. For redefining where cancer begins, how it evolves and why eradication may be less important than systemic modulation.

Paradigm shifts are slow. They emerge as clinicians begin to see differently—and insist that the contradictions, anomalies and paradoxes are not background noise, but signal.

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